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| Notes | Collaborative efforts with |
| Found By | Karen Holmes |
| Dates | |

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Letterman & Mt. Zion on drug radiation interactions and dose rate damage in skin. See 2nd pg. 2nd paragraph

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THE UNIVERSITY OF ARIZONA

ARIZONA MEDICAL CENTER
TUCSON, ARIZONA 85724

COLLEGE OF MEDICINE
DIVISION OF RADIATION ONCOLOGY

December 19, 1975

Dr. Ed Alpen, Director
Donner Laboratory of Medical Physics
University of California
Berkeley, California 94720

Dear Dr. Alpen:

Dr. Tobias has requested that I outline for you the projects that I was involved in while at the Lawrence Berkeley Laboratory. My particular group received support from three agencies, ERDA, NCI and NASA and different facets of work were considered under the different agencies.

ERDA: The basic approach for the ERDA directed work dealt with growth control mechanisms in skin, and skin carcinogenesis after irradiation, as described in our last 189 form. A paper on changes in growth control mechanisms (chalones) as a function of age in mice has recently been submitted to Cell and Tissue Kinetics. This portion of the work was handled primarily by myself. We also were to begin a program studying the incidence of corneal tumors in mice after exposure to different high LET particles (in particular helium ions) with the intent of correlating tumor incidence to production of chromosomal aberrations, but this work had not yet begun.

NCI: Our primary effort in the last few years has gone into developing a program to study effects of high LET particles on normal tissues in regard to Dr. Tobias' pretherapeutic grant. In this regard, I feel that we have been quite successful in developing baseline systems and we have already gathered quite a lot of data.

We have done much work on skin (mice, hamsters, rats) as it is an easy, reproducible assay system that appears to predict quite well for patient therapy (at least for neutron studies), the changes in the RBE and repair characteristics after different types of radiation, both for single and fractionated doses. This work has been in collaboration with Kay Woodruff and John Lyman, and our initial single dose response data to neon ion irradiation will appear in February's Radiation Research. We also recently completed an experiment assaying sublethal damage repair in mouse skin after split doses of neon ions in the spread-out Bragg of neon ions. The data indicate a

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single dose RBE of about 2.5 with about a 75% reduction (as compared to 230KV x-rays) in sublethal damage repair capability. These mice should be kept for at least another 100 days so that late damage to the irradiated area may also be assessed.

With regard to effects on skin, other collaborative efforts have been with Dr. Bernard S. Lewinsky, Letterman Army Medical Center, Presidio of San Francisco. This work has involved studies of drug-radiation interactions; in particular we have studied the effects of bleomycin on skin radiation sensitivity and repair of sublethal damage. Also, I have worked with Dr. Donald Baker of Mt. Zion Hospital, San Francisco, studying the effects of dose rate on early and late damage in skin.

Another major effort has gone into studying the effects of radiation on rat spinal cord as a model for radiation damage to a "dose-limiting" system. We have performed both single and fractionated experiments at the LBL 184-inch cyclotron and have defined the tolerance response for spinal cord - which is quite a bit different than that of skin. I have talked at length with Jack Fowler of the Gray Laboratory England about the dose effect curve, and the data may suggest that the "survival" curve for this essentially nonproliferating organ system starts off with a zero (or very small) initial slope. If so, this may be exploitable in terms of the difference between various normal tissues and tumors. We have also performed several sets of single dose irradiations to plateau region neon ions in rats and have obtained a single dose RBE of 1.3. This data will be published shortly in Int. J. Radiat. Biol. These are difficult experiments as the animals should be kept 8-12 months post irradiation to insure that all animals have responded. This work has been done in collaboration with Woodruff, Lewinsky, and Lyman.

As another model of late radiation damage, we have begun studies in hamster lung. This work is primarily anatomical in nature and is under the direction of Kay Woodruff. However, we have been involved in the irradiations and animal sacrifice. Animals have been irradiated with both single and fractionated (2 week interval) doses of x-rays and neon ions, and a group of animals has also been irradiated with helium ions. We felt that the hamster was the best model for chronic damage to lung tissue and for future biochemical studies.

We have begun a project collaborating with Dr. Eli Glatstein of Stanford University School of Medicine, Palo Alto, Calif. looking at effects of various radiations on the kidneys of mice and rats. We had done one experiment to date at the LBL-184-inch cyclotron. This project will primarily be under the direction of Dr. Glatstein.

Another area of collaboration that was working out extremely well was with the Naffziger Laboratory for Neurological Research, Univ. Cal., San Francisco under the direction of Dr. C.B. Wilson. In particular, my direct association was with Dr. Ken Wheeler. In 1973, I was able to develop a technique for dissociating an in vivo solid brain tumor that

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their group was using for intracerebral survival studies into single cells which would then form colonies in tissue culture. This allowed us a direct estimate of the effects of radiation on the clonogenic cell survival of the intracerebral solid tumor. Much work has been done on the survival responses ofoxic and hypoxic tumors to both x-ray and neon ions, and a paper on the neon ion effects has recently appeared in the Int. J. of Radiat. Biol. This is one of the few tumor systems that allows such an in vivo to in vitro survival assay (similar to the Rhodomyosarcoma tumor system of S. Curtis) and presents an excellent means of assessing high LET radiation effects. A graduate student, Ms. Pepi Ross has also been involved heavily in this work, and has been investigating the effects of hyperthermic treatment of these cells in vitro.

NASA: The work involved in the NASA area has primarily been involved with the assessment of ionizing radiation on the retina of Necturus maculosus and mice. To date, primarily a graduate student, Mr. Michael Malachowski, has been involved in this work. He has been preparing scanning electron micrographs of irradiated Necturus retinas, and by use of a arbitrary grading system has been able to obtain initial RBE data on helium and neon ion effects. This work also is intended to include transmission electron microscopic data, but this aspect has been quite hampered by the lack of trained, available technician time to prepare samples. Mr. Malachowski also intends to perform gross ERG measurements on in vitro retina with the intent of correlating electrophysiology to structural alterations. This work must be considered as primarily a Ph.D. thesis project. An area that I have been involved in is the labeling of rods and cones in mouse eye with a triated phenylamine-leucine mixture. The intent being to measure the transit time of the retinal elements (about 10 days in the mouse) and to examine impairment of protein synthesis by ionizing radiation.

In all of the above work, the technician who worked for me, Ms. Patti Smith, has been extremely involved. She is extremely competent and is currently writing up a paper that I allowed her to do on her own, on the effects of various lipids on radiation damage and repair in skin.

Future work.

ERDA: The skin work should probably concentrate more heavily on mechanisms involved and incidences of tumors in small animals after exposure to various high LET particles. It would be of interest to examine tumor incidence after exposure to particles of the same LET but different atomic number to study effects of track structure on tumorigenesis. The corneal tumor-chromosome aberration study could be handled by a graduate student.

NCI: Due to the restriction of relatively low intensity beams (neon, argon) much of the immediate future work will still be done with localized irradiation of small animals. With regard to skin

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studies, work needs to be done on late effects, and on fractionated responses in both the plateau and spread-out Bragg peak region of ionization; for neon, argon and possibly carbon ions. Much work should be done on the spinal cord, both in terms of single and fractionated dose responses, and in terms of the mechanism of damage. I feel that I may have a way to examine biochemically the possible modes of damage by looking at various enzymes in spinal cord tissue. The biochemical and dose response relationships of high LET radiations in spinal cord is a project of particular interest to me, and I intend to submit a proposal to NCI to continue this work. Other areas of interest in spinal cord studies would be, for example, to examine if spinal cord exhibits the phenomenon of slow repair as does lung tissue. Indeed, we have a pilot study ongoing at Berkeley looking at the effects of long term split doses (from days to months) on spinal cord to see if such slow repair can be found. This program is currently under the direction of Kay Woodruff and Bernard Lewinsky. The lung research is currently under good supervision from Kay Woodruff, and enough animals have been irradiated for the immediate future. However, again future experiments will involve argon ions in particular, and probably a more biochemical approach will be needed for subsequent years.

The above is a rough outline of the current work and outside collaboration. I would certainly be glad to discuss these with you in more detail at any time. I have a strong personal interest in the High LET radiation biology program at Berkeley and would be glad to assist in any way possible.

I thank you for your consideration.

Sincerely yours,

John T. Leith

John T. Leith, Ph.D.

cc: Dr. C.A. Tobias
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